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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/606,630	06/26/2003	Spiros Liras	PC10085C	4988
23913	7590	06/03/2004	EXAMINER	
PFIZER INC 150 EAST 42ND STREET 5TH FLOOR - STOP 49 NEW YORK, NY 10017-5612			MCKENZIE, THOMAS C	
			ART UNIT	PAPER NUMBER
			1624	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/606,630

Applicant(s)

LIRAS ET AL.

Examiner

Thomas McKenzie, Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>6/26/03</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to an application filed on 6/26/03. There are twenty-one claims pending and twenty-one under consideration. Claims 1-13 are compound claims. Claims 14, 15, 18, and 19 are composition claims. Claims 16, 17, 20, and 21 are method of using claims. This is the first action on the merits. The application concerns some bis-phenyl piperidine and morpholine compounds, compositions, and uses thereof.

2. The PTO no longer follows the practice of holding indefinite the phrase "such as" or its Latin equivalent "e.g." an abbreviation of "exempli gratia", when it is clear that the usage is illustrative of the preceding word. Thus, Applicants usage of e.g. in claim 1 will not be rejected.

Priority

3. The status of all nonprovisional parent applications referenced should be included. Please amend the first line of the specification to reflect the issuance of US Patent No. 6,586,431 from the parent of the present application. Please amend the first line of the specification to reflect the issuance of US Patent No. 6,503,905 from the grandparent of the present application.

Claim Objections

4. Objection is made to claims 18 and 19 under 37 CFR 1.75 as being duplicates of claims 14 and 15 respectively. When two claims in an application are duplicates it is proper after allowing one claim to object to the other as being a

substantial duplicate of the allowed claim. See MPEP § 706.03(k). These appear to be word for word duplicates.

5. Objection is made to claims 15, 18, and 19 under 37 CFR 1.75 as being a substantial duplicate of claim 14. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The phrase "for treating a disorder ... etc." is a statement of intent. This is a purely mental act with no physical consequences. Thus, claims 15, 18, and 19 are composition claims with the same limitations as claim 14.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation

given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1, lines 25 and 30, page 55 and lines 11, 12, and 18, page 56 recites the broad recitation "one to seven" and the claim also recites "(preferably ...", which is the narrower statement of the range/limitation.

7. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claim 1, the abbreviation "i.e." in line 26, page 55 renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). The abbreviation "i.e." stands for "id est," which means, simply, "that is" or "which is to say." Thus, "i.e." introduces a definition or a clarification:

"Larry was still dressed in his work clothes, i.e., a clown suit." Is the halogen astatine included or not?

8. Claims 14, 16, 18, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 14, lines 13, 18, and 19, page 57, claim 16 lines 29 and 35, page 57, claim 18 lines 10 and 17, page 58, and claim 20, lines 28, and 32, page 58 recites

the broad recitation "inflammatory disease", "addictions" etc. and the claim also recites "such as arthritis ..." "e.g. additions to or dependencies on alcohol ..." etc. which are the narrower statement of the range/limitation.

9. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Upon which claim does this claim depend?

10. Claims 17 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify "a disorder or condition, the treatment or prevention of which can be effected or facilitated by modulating binding to opioid receptors in a mammal". It is unclear what diseases and treatments applicant is intending to encompass. For example, in lines 15-19, page 7 Applicants discuss such diseases but do not list what they are specifically or describe how they can be identified. Determining whether a given disease responds or does not respond to such a receptor antagonist and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases

Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pain, does not reasonably provide enablement for treating all other listed diseases. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The issue is the correlation between clinical

efficacy for disease treatment and Applicants' δ -opioid receptor assay and very broad scope of the diseases to be treated.

a) Determining if any particular claimed compound would treat any particular claimed disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large quantity of experimentation. b) The direction concerning treating diseases is found in the passage spanning line 32, page 2 to line 10, page 3, lines 7-22, page 6, and lines 22-34, page 8, which merely states Applicants' intention to do so. Applicants describe formulations in the passage spanning line 6, page 33 to line 10, page 34. Doses required to practice their invention are described in lines 11-15, page 34. A 50,000-fold range of doses is recommended. Since no δ -opioid receptor ligand has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There is an *in vitro* receptor binding assay described in line 19, page 30 to line 13, page 31 with no data. There are two *in vitro* organ bath assays described in lines 16-38, page 31 with no data. There is an *in vitro* cell function assay described in line 5, page 32 to line 6, page 33, again with no data. Applicants do not assert and it is not recognized in the

pharmaceutical arts that these assays are correlated to clinical efficacy for treatment of all claimed diseases. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease with inhibitors of the δ -opioid receptor, which involves physiological activity. e) The state of the clinical arts in δ -opioid receptor diseases is provided by Kowaluk (Ann. Reports Med. Chem.) who reports in the second complete paragraph on page 12, that analgesia is the only recognized use of such agonists. Applicants in lines 25-30, page 1 admit that pain relief is the only art recognized useage.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the hundreds of thousands of compounds of claim 1 as well as the hundred of diseases embraced by the term inflammatory disease, gastrointestinal disorders etc. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the

time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

12. Claims 15, 19, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating specific diseases, does not reasonably provide enablement for preventing diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the piperidine and morpholine compounds such as present here. In addition, it is presumed that “prevention” of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

The factors to be considered in making an enablement rejection have been summarized above. 1) As discussed above, preventing diseases requires

identifying those patients who will acquire the disease before symptoms occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage spanning line 32, page 2 to line 10, page 3, lines 7-22, page 6, and lines 22-34, page 8, lists the diseases Applicant intend to treat. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical medicine and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become sufferers of the many claimed diseases before the fact. 6) The artisan using Applicants invention would be a Board Certified physician with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of the claimed diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent the claimed diseases generally.

That is, the skill is so low that no compound effective generally against all the claimed disorders has ever been found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by Formula I.

The Examiner suggests deletion of the word "prevention".

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,503,905. Although the conflicting claims are not identical, they are not patentably distinct from each other because the definition of variables R^1 , R^3 , X, Q, Z^1 , and Z^2 are identical in the two claims 1. R^2 in U.S. Patent No. 6,503,905 excludes hydrogen, presently claimed, and limits the Markush group to that of the present claim 7 when Q is CH_2 . The active compounds contained in U.S. Patent No. 6,503,905 provide the guideposts to make the selections required to arrive at the present compound claims. Pharmaceutical compositions and treatment of diseases including asthma are found in claims 7 and 8 of U.S. Patent No. 6,503,905. Thus, Applicants claims 14-21 are made obvious as well.

14. Claims 16, 17, 20, and 21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,586,431. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issue of the structural variations

was discussed above. Claim 1 of U.S. Patent No. 6,586,431 is drawn to treatment of addiction. Addiction is one of the many treatments presently claimed. This is a species-genus situation. According to the MPEP §806.04(i) "Generic Claims Presented for First Time After Issue of Species. The Office no longer follows the practice of prohibiting the allowance of generic claims that are presented for the first time after the issuance of a copending application claiming plural species. Instead, the Office may reject the generic claims on the grounds of obviousness-type double patenting. Applicant may overcome such a rejection by filing a terminal disclaimer. See *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29."

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

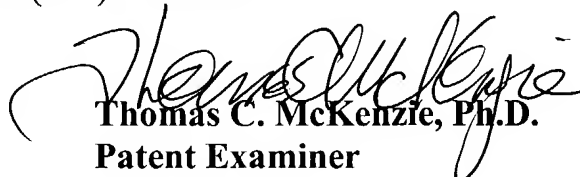
Claims 1-3, 6, 16, 17, 20, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Kametani (Yakugaku Zasshi). The compounds 6, 3a, and 3b fit formula (I) with R^1 = hydrogen, benzyl or cyclopropylmethyl, $Q = CH_2$, $X = CH$, $R^2 = Z^1 = Z^2$ = hydrogen, and R^3 = hydroxyl. They are found in Chart 2, page 1490 of the reference. The abstract of the reference states the expectation that

compounds 3a and 3b are analgesics. Thus, Applicants' treatments claims concerning pain and disorders related to opioid receptors are taught.

Conclusion

16. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

17. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.


Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624